REMARKS

Claims 41-62 are pending in the application and have been rejected. Claims 42, 49-54, and 58 have been canceled without acquiescence to the Examiner's rejections, without abandonment of the invention of the canceled claims, and without prejudice to applicants to seek patent protection for the subject matter of the canceled claims by filing one or more applications for patent in the future. Claims 43-47, 55-57, and 59-62 have been amended to remove their dependencies to the canceled claims. Reconsideration and allowance of Claims 41, 43-48, 55-57, and 59-62 in view of the above amendments and following remarks is respectfully requested.

The Claimed Invention

Claims 41, 43-48, 55-57, and 59-62 are pending. Claims 41 and 48 are the pending independent claims.

Claim 41 is directed to a method for increasing adiponectin production that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 43-47, 57, 59, and 60 depend from Claim 41.

Claim 48 is directed to a method for treating hypoadiponectinemia that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 55-57, 61, and 62 depend from Claim 48.

Entry of the Amendment

Entry of the amendment is respectfully requested. The amendment cancels rejected Claims 42, 49-54, and 58, and amends Claims 43-47, 55-57, and 59-62 to remove their dependencies to the canceled claims. The amendments do not add new matter, the amendments do not raise new issues that would require further search and/or consideration by the Examiner, and the amendments do place the application in condition for allowance. Accordingly, entry of the amendment is requested.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Examiner Interview Summary

Applicants' attorney acknowledges with appreciation the interview with the Examiner and his supervisor, Examiner Wang, on May 2, 2008. In the interview, the Section 112 enablement rejections and the Section 103 prior art rejection were discussed.

As an initial matter, Examiner Betton agreed that the Section 112 rejection, which begins with a statement regarding inhibiting amyloidosis, is a typographical error and has no place in the Office Action. See the paragraph spanning pages 6 and 7 in the Office Action dated February 8, 2008. We believe that the statement regarding amyloidosis is a cut-and-paste error made by the Examiner.

We confirmed that the Examiner is unwilling to permit the use of the transition "consisting essentially of" for the reasons set forth in the Office Action. The Examiner also confirmed his concern that the specification lacks guidance for identifying a population of subjects suffering from syndrome X. We acknowledged the Examiner's concern and noted that we believe that the skilled person would be able to make the identification and that, therefore, our arguments set forth in our previous response reflected our position regarding this enablement.

Applicants' attorney explained that the pending claims in the application could be considered to be directed to two types of methods: (1) a method for increasing adiponectin production (Claim 41) and a method for treating hypoadiponectinemia (Claim 48); and (2) methods for treatment of various conditions (Claims 42 and 49-54). Applicants' attorney noted that the rejection of claims set forth in the Office Action appeared to relate more to the method of treatment claims rather than the methods for increasing adiponectin production and the treatment of hypoadiponectinemia.

Regarding the Section 112 enablement rejection, applicants' attorney stated that the rejection appeared to have some relevance to the method of treatment claims, but not to the claims directed to increasing adiponectin production and the treatment of hypoadiponectinemia.

Regarding the Section 103 rejection, applicants' attorney noted that the Lohray and Ikeda references were directed to combination therapies in which one of the administered components can be an HMG CoA reductase inhibitor. Applicants' attorney further noted that the Examiner sought to link the use of HMG CoA reductase inhibitors and adiponectin production through the motivation provided by the Schulze reference. Applicants' attorney referred the Examiner to the second paragraph on page 5 of the Office Action dated February 8, 2008. Applicants' attorney noted that in that in applicants' previous response it was argued that the Schulze reference did not provide the motivation and establish a link between HMG CoA reductase inhibitors and adiponectin, and requested that the Examiner provide evidence to support his position of the existence of such a link. Applicants' attorney then called the Examiner's attention to the third paragraph on page 5 of the Office Action dated February 8, 2008, where he provided evidence of the link by citing the Kadowaki and Saito references and stating that those references further substantiated the teaching of the Schulze reference. Applicants' attorney pointed out to the Examiners that each of these references has a publication date later than the filing date of the international application that forms the basis of the pending U.S. application. The Schulze reference has a publication date of 2005, the Kadowaki reference has a publication date of 2005, and the Saito reference has a publication date of 2007. Applicants' attorney stated that the evidence that the Examiner used to link adiponectin production to the administration of an HMG CoA reductase inhibitor was not prior art citable against the claimed invention. The Examiners agreed that these references have publication dates later than the effective filing date of the present application.

Applicants' attorney noted that the evidence provided by the Examiner actually supports the novelty and non-obviousness of the claimed invention. Applicants' attorney concluded by reiterating that the present application provides the first demonstration of the administration of an HMG CoA reductase inhibitor to increase adiponectin production and to treat hypoadiponectinemia.

The interview concluded by the Examiners saying that they would consider the points raised in the interview and telephone applicants' attorney on May 5 with their further consideration. Examiner Betton left a voicemail for applicants' attorney on May 27, 2008, indicating that he had nothing to add to the telephone interview. To date, applicants have not received the Examiner's Interview Summary.

The Rejection of Claims 41-62 Under 35 U.S.C. § 112, First Paragraph

Claims 41-62 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to enable the skilled person to use the invention commensurate in scope with the claims. Withdrawal of the rejection is requested for the following reasons.

As an initial matter, we note that the Section 112 rejection begins with a statement regarding inhibiting amyloidosis. See the paragraph spanning pages 6 and 7 in the Office Action dated February 8, 2008. As discussed in the Examiner's Interview, the statement regarding amyloidosis has no place in the Office Action.

The Examiner further states that the specification fails to teach how to determine and select the population of individuals with or without the recited conditions. According to the Examiner, it is not clear what parameters one skilled in the art would use in order to identify a subject in which the disease could be prevented. In addition, the Examiner states that there is insufficient evidence in the specification that the diseases identified in the claims would be inhibited with the administration with one or more of HMG-CoA reductase inhibitors.

Claims 42, 49-54, and 58, directed to various diseases and conditions, have been canceled.

Claims 41 and 48 are the remaining pending independent claims. Claim 41 is directed to a method for increasing adiponectin production that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 43-47, 57, 59, and 60 depend from Claim 41. Claim 48 is directed to a method for treating hypoadiponectinemia that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 55-57, 61, and 62 depend from Claim 48.

Regarding Claim 41 and its dependent claims, the Examiner's concern regarding identifying a subject population for treatment is not relevant to the recited method for increasing adiponectin production. The skilled person can determine those having depressed adiponectin level and then address that deficiency by the claimed method.

Similarly, with regarding to Claim 48, applicants submit that it is well within the purview of the skilled person to diagnose a person suffering from depressed adiponectin level (hypoadiponectinemia) and then address that deficiency by the claimed method.

Hypoadiponectinemia is a well-known condition that is readily identified and diagnosed by a person skilled in the art (i.e., a medical doctor in the relevant field). The application has provided sufficient support for the inhibitory effect of HMG-CoA reductase inhibitors on the diseases recited in Claims 41 and 48, as evidenced by Example 1, "Adiponectin production enhancing action (in vitro)," and Example 2, "Adiponectin production enhancing action (in vivo) and glucose uptake enhancing action." Furthermore, M.P.E.P. 2164.02 titled "Working Example" allows the correlation between *in vitro* and *in vivo* animal model assays and a claimed method of use "if the art is such that a particular model is recognized as correlating to a specific condition."

In applicants' response filed November 20, 2007, the Examiner was provided evidence of the relationship between adiponectin and certain diseases: (1) Pathophysiological significance of

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

adiponectin, Shimomura et al., *Med Mol Morphol* 2007 40:55-67, attached in the previous response as **Exhibit A**; and (2) Adiponectin and Cardiovascular Disease, Han et al., *J Am Coll Cardiol* 2007 49:531-538, attached in the previous response as **Exhibit B**.

The Shimomura publication shows the clinical significance of adiponectin and the relationship between adiponectin and several diseases (obesity, cardiovascular disease, hypertension and dyslipidemia, metabolic syndrome, inflammation, cancer and other diseases). See pages 58 and 59. The Han publication describes the relationship between adiponectin and cardiovascular disease.

As evidenced by these publications, the skilled person would understand that the experimental results set forth in the application as originally filed establish the correlation between the *in vitro* and *in vivo* animal model assays in the application and the claimed methods.

Because the application as originally filed provides a disclosure that enables the skilled person to make and use the claimed invention, the application satisfies the enablement requirement. Withdrawal of the rejection is requested.

The Rejection of Claims 41-62 Under 35 U.S.C. § 103(a)

Claims 41-62 have been rejected under 35 U.S.C. § 103(a) as being unpatentable as obvious over the combined teaching of U.S. Patent No. 6,130,214, issued to Lohray et al., in view of U.S. Patent No. 6,384,062, issued to Ikeda et al. The Examiner further relies on Schulze et al., "Adiponectin and Future Coronary Heart Disease Events Among Men With Type 2 Diabetes," *Diabetes 54*:534-539, 2005, printed pages 1-6.

As noted above, Claims 42, 49-54, and 58 have been canceled. Claims 41 and 48 are the remaining pending independent claims. Claim 41 is directed to a method for increasing adiponectin production that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 43-47, 57, 59, and 60 depend from Claim 41. Claim 48 is directed to a

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

method for treating hypoadiponectinemia that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 55-57, 61, and 62 depend from Claim 48.

The Cited References. The Lohray reference relates to antiobesity and hypocholesterolemic compounds. Specifically, the Lohray reference discloses novel β-aryl-α-oxysubstituted alkylcarboxylic acids (benzothiazin and benzoxazin derivatives) having a specified formula. The Lohray reference states at Col. 2, lines 1-3, that its compounds, in combination with one or more HMG-CoA reductase inhibitors, are useful in the treatment and/or prophylaxis of a variety of diseases.

The Ikeda reference relates to pharmaceutical compositions that include an insulin sensitivity enhancer in combination with other antidiabetics (e.g., a HMG-CoA reductase inhibitor such as pravastatin) that differ from the enhancer in the mechanism of action. The compositions show a depressive effect on diabetic hyperglycemia and are useful for prophylaxis and treatment of diabetes and diabetes complications.

The Schulze reference relates to the relationship between adiponectin and the future coronary heart disease (CHD) events among men with Type 2 diabetes and describes the association between plasma adiponectin levels and incidence of CHD. The results set forth in the reference suggest that increased adiponectin levels are associated with moderately decreased CHD risk in men.

The Lohray and Ikeda references each describe administering a HMG-CoA reductase inhibitor or a statin in combination with a second therapeutic drug to treat a condition: the Lohray reference describes administering one or more HMG-CoA reductase inhibitors in combination with a novel benzothiazin or benzoxazin derivative to treat a variety of conditions; and the Ikeda reference describes administering a statin (a HMG-CoA reductase inhibitor) in combination with a novel insulin sensitivity enhancer compound to treat diabetes and diabetes complications.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Independent Claims 41 and 48. Claims 41 and 48 are directed to methods for increasing adiponectin production and hypoadiponectinemia, respectively. Each method includes the step of administering an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal in need of such treatment. Claim 48 further recites that the HMG-CoA reductase inhibitor is water soluble.

Neither the Lohray nor Ikeda references describes, teaches, or suggests in any way a method for either increasing adiponectin production or treating hypoadiponectinemia. As noted above, the Lohray reference describes novel β-aryl-α-oxysubstituted alkylcarboxylic acids for use in the treatment of hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases, familial hypercholesterolemia, hyperglyceridemia, lowering of atherogenic lipoproteins, very low density lipoprotein, and LDL, renal diseases including glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, and nephropathy, insulin resistance, leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, and other cardiovascular disorders, improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome, inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma, and cancer (see Col. 1, lines 43-67). The reference also states that the novel compounds are useful in the treatment of those diseases in combination with one or more HMG-CoA reductase inhibitors (see Col. 2, lines 1-3).

As noted above, the Ikeda reference describes pharmaceutical compositions that include an insulin sensitivity enhancer in combination with other antidiabetics that differ from the enhancer in the mechanism of action for use in treating diabetes and diabetes complications including diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia (see Col. 18, lines 1-6).

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Unlike the Lohray and Ikeda references, the claimed invention do not recite a combination therapy. Furthermore, neither reference describes, teaches, or suggests the claimed invention: a method for increasing adiponectin production or a method for treating hypoadiponectinemia that includes the step of administering one or more HMG-CoA reductase inhibitor(s).

The Schulze, Kadowaki, and Saito References. The Examiner sought to link the use of HMG CoA reductase inhibitors and adiponectin production through the motivation provided by the Schulze reference. See the second paragraph on page 5 of the Office Action dated February 8, 2008. According to the Examiner, the Schulze reference discloses adiponectin as a major modulator of insulin resistance and dyslipidemia, mechanisms that are associated with increased atherosclerotic risk in diabetic patients.

Applicants argued in their previous response that the Schulze reference did not provide the motivation to combine nor establish a link between HMG CoA reductase inhibitors and adiponectin. Applicants requested that the Examiner provide evidence to support the position of the existence of such a link. In the third paragraph on page 5 of the Office Action dated February 8, 2008, the Examiner indicated that evidence of the link could be found in the Kadowaki and Saito references and stated that those references further substantiated the teaching of the Schulze reference.

However, each of the references noted by the Examiner has a publication date later than the filing date of the international application that forms the basis of the pending U.S. application. The Schulze reference has a publication date of 2005, the Kadowaki reference has a publication date of 2005, and the Saito reference has a publication date of 2007. Because the evidence that the Examiner has used to link adiponectin production to the administration of an HMG CoA reductase inhibitor are references having publication dates later than the effective

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

filing date of the present application, the references are not citable as prior art against the claimed invention.

Applicants maintain that the evidence provided by the Examiner further supports the novelty and non-obviousness of the claimed invention. Applicants reiterate that the present application provides the first demonstration of the administration of an HMG CoA reductase inhibitor to increase adiponectin production and is effective in treating hypoadiponectinemia.

Applicants respectfully submit that the Examiner has failed to provide or establish any link between adiponectin production and HMG-CoA reductase inhibitors. Because the cited references fail to teach or suggest a method for increasing adiponectin production (Claim 41) or a method for treating hypoadiponectinemia (Claim 48), applicants submit that the claimed invention is non-obvious and patentable over the cited references. Withdrawal of the rejection is requested.

CONCLUSION

In view of the above amendments and foregoing remarks, Claims 41, 43-48, 55-57 and 59-62 are believed to be in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS^{PLLC}

George E. Renzoni, Ph.D.
Registration No. 37,919
Direct Dial No. 206.695.1755

GER:md

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS^{PLLC}
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100